



US008754091B2

(12) **United States Patent**  
**Honigberg et al.**(10) **Patent No.:** **US 8,754,091 B2**  
(45) **Date of Patent:** **\*Jun. 17, 2014**(54) **INHIBITORS OF BRUTON'S TYROSINE KINASE**(75) Inventors: **Lee Honigberg**, San Francisco, CA (US); **Erik Verner**, Belmont, CA (US); **Zhengying Pan**, Austin, TX (US)(73) Assignee: **Pharmacyclics, Inc.**, Sunnyvale, CA (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/542,440**(22) Filed: **Jul. 5, 2012**(65) **Prior Publication Data**

US 2012/0277254 A1 Nov. 1, 2012

**Related U.S. Application Data**

(60) Continuation of application No. 13/479,053, filed on May 23, 2012, which is a continuation of application No. 13/472,292, filed on May 15, 2012, which is a continuation of application No. 13/450,158, filed on Apr. 18, 2012, which is a continuation of application No. 13/361,733, filed on Jan. 30, 2012, now Pat. No. 8,399,470, which is a continuation of application No. 13/340,556, filed on Dec. 29, 2011, which is a continuation of application No. 13/340,409, filed on Dec. 29, 2011, which is a continuation of application No. 13/335,719, filed on Dec. 22, 2011, which is a continuation of application No. 13/328,718, filed on Dec. 16, 2011, now Pat. No. 8,476,284, which is a continuation of application No. 13/312,606, filed on Dec. 6, 2011, now Pat. No. 8,497,277, which is a continuation of application No. 13/249,066, filed on Sep. 29, 2011, which is a continuation of application No. 12/356,498, filed on Jan. 20, 2009, now Pat. No. 8,088,781, which is a division of application No. 11/617,645, filed on Dec. 28, 2006, now Pat. No. 7,514,444.

(60) Provisional application No. 60/826,720, filed on Sep. 22, 2006, provisional application No. 60/828,590, filed on Oct. 6, 2006.

(51) **Int. Cl.****A01N 43/90** (2006.01)**A61K 31/519** (2006.01)**C07D 487/00** (2006.01)(52) **U.S. Cl.**USPC ..... **514/262.1**; 544/262(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**5,397,787 A 3/1995 Buzzetti et al.  
6,160,010 A 12/2000 Uckun et al.  
6,221,900 B1 4/2001 Uckun et al.  
6,326,469 B1 12/2001 Ullrich et al.  
6,506,769 B2 1/2003 Snow et al.6,660,744 B1 12/2003 Hirst et al.  
6,753,348 B2 6/2004 Uckun et al.  
6,770,639 B2 8/2004 Snow et al.  
6,921,763 B2 7/2005 Hirst et al.  
7,138,420 B2 11/2006 Bentzien et al.  
7,332,497 B2 2/2008 Hirst et al.  
7,514,444 B2\* 4/2009 Honigberg et al. .... 514/263.22  
7,718,662 B1 5/2010 Chen  
7,732,454 B2\* 6/2010 Verner ..... 514/262.1  
7,741,330 B1 6/2010 Chen  
7,825,118 B2\* 11/2010 Honigberg et al. .... 514/249  
7,960,396 B2\* 6/2011 Honigberg et al. .... 514/262.1  
8,008,309 B2 8/2011 Honigberg et al.  
8,088,781 B2 1/2012 Honigberg et al.  
8,158,786 B2 4/2012 Honigberg et al.  
8,232,280 B2\* 7/2012 Honigberg et al. .... 514/262.1  
8,236,812 B2\* 8/2012 Honigberg et al. .... 514/265.1  
2002/0016460 A1 2/2002 Snow et al.  
2002/0155505 A1 10/2002 Wells et al.  
2003/0013125 A1 1/2003 Braisted et al.  
2003/0040461 A1 2/2003 Mcatee  
2003/0125235 A1 7/2003 Foxwell  
2004/0006083 A1 1/2004 Hirst et al.  
2005/0008640 A1 1/2005 Waegell et al.  
2005/0084905 A1 4/2005 Prescott et al.  
2005/0090499 A1 4/2005 Currie et al.

(Continued)

**FOREIGN PATENT DOCUMENTS**EP 1473039 11/2004  
WO WO-97-28161 8/1997

(Continued)

**OTHER PUBLICATIONS**U.S. Appl. No. 14/033,344, filed Sep. 20, 2013, Honigberg et al.  
U.S. Appl. No. 13/952,531, filed Jul. 26, 2013, Honigberg et al.  
U.S. Appl. No. 13/965,135, filed Aug. 12, 2013, Buggy et al.  
U.S. Appl. No. 13/526,161 Final Office Action mailed May 15, 2013.  
U.S. Appl. No. 13/526,163 Final Office Action mailed May 15, 2013.  
U.S. Appl. No. 13/249,066 Final Office Action mailed May 15, 2013.  
EP 12172842.2 Extended Search Report dated May 14, 2013.  
U.S. Appl. No. 13/341,695 Final Office Action mailed Jun. 7, 2013.  
U.S. Appl. No. 13/439,775 Final Office Action mailed Jun. 17, 2013.  
U.S. Appl. No. 13/607,036 Final Office Action mailed Jun. 24, 2013.  
U.S. Appl. No. 12/594,805 Final Office Action mailed Jun. 27, 2013.

(Continued)

*Primary Examiner* — Jeffrey H Murray(74) *Attorney, Agent, or Firm* — Wilson, Sonsini, Goodrich & Rosati(57) **ABSTRACT**

Disclosed herein are compounds, including compounds having the structure of Formula (A), (B), (C), and (D), as described in further detail herein, that form covalent bonds with Bruton's tyrosine kinase (Btk). Also described are irreversible inhibitors of Btk. Methods for the preparation of the compounds are disclosed. Also disclosed are pharmaceutical compositions that include the compounds. Methods of using the Btk inhibitors are disclosed, alone or in combination with other therapeutic agents, for the treatment of autoimmune diseases or conditions, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.

**21 Claims, 8 Drawing Sheets**